REMARKS

Status of the Claims

Claims 82-84 and 87-94 are pending. In the non-final Office Action dated December 24, 2008, the Office maintains rejections of Claims 82-84 and 87-94 under 35 U.S.C. § 103 and under the judicially created doctrine of obviousness-type double patenting.

By this response, Applicants amend Claim 82 so that the phrase "comprises SEQ ID NO:16" is now "consists of SEQ ID NO:16."

No new matter is added by way of claim amendment. Applicants respectfully request reconsideration of the claims in view of the remarks below. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

The Office maintains a rejection of Claims 82-84 and 87-92 as obvious over WO 99/07210 by Stomp *et al.* in view of Buzby *et al.*(1990) *Plant Cell* 2:805-814; Wong *et al.* (1992) *Plant Mol. Biol.* 20:81-93; and Stiekema *et al.* (1983) *Nucleic Acids Res.* 11:8051-8061. In support of the Office's rejection, the Examiner alleges that although Stomp *et al.* did not teach enhanced protein expression in duckweed with an expression cassette having a 5' leader sequence of SEQ ID NO:16, one of ordinary skill in the art would find it obvious to do so after reading Buzby *et al.* and Wong *et al.* This rejection is respectfully traversed.

The Office likewise maintains a rejection of Claims 82-84 and 87-94 as obvious over Stomp *et al.*, *supra*, in view of Buzby *et al.*, *supra*; Wong *et al.*, *supra*; U.S. Patent No. 5,460,952 to Yu *et al.*; Park *et al.* (1997) *J. Biol. Chem.* 272:6876-6881; and Stiekema *et al.*, *supra*. In support of the Office's rejection, the Examiner alleges that although Stomp *et al.* did not teach enhanced protein expression in duckweed with an expression cassette having a 5' leader sequence of SEQ ID NO:16 or a signal peptide from rice α-amylase gene (SEQ ID NO:6), one of ordinary skill in the art would find it obvious to do so after reading Buzby *et al.*, Wong *et al.*, Yu *et al.* and Park *et al.* This rejection is likewise respectfully traversed.

Applicants address the rejections together below because each relies upon common, principal citations (*i.e.*, Stomp *et al.*, Buzby *et al.* and Wong *et al.*). In contrast to the cited references relied upon by the Examiner, Applicants were the first to appreciate that SEQ ID

NO:16 alone can enhance protein expression in duckweed and are entitled to claims directed thereto. Consequently, the Examiner fails to present a *prima facie* case of obviousness by not providing sufficient evidence showing that one of ordinary skill in the art could reliably predict the effect of SEQ ID NO:16 on polypeptide expression in duckweed in view of the cited references.

Establishing a *prima facie* case of obviousness requires an assessment of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), which provides a framework for applying the statutory language of § 103 (*i.e.*, the "Graham Factors"). Under the "Graham Factors," an examiner must:

1. Determine the scope and content of the prior art;
2. Ascertain the differences between the prior art and the claims at issue;
3. Resolve the level of ordinary skill in the pertinent art; and
4. Consider any relevant secondary considerations.

Recently, the Supreme Court identified seven (7) rationales for use in supporting obviousness determinations, which are consistent with *Graham*. MPEP § 2143. Regardless of the applied rationale, prior art "can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success." MPEP § 2143.02 I. The reasonable expectation of success is not required to be absolute (MPEP § 2143.02 II.), but must be determined at the time the invention was made (MPEP § 2143.02 III.). Thus, "evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." MPEP § 2143.02.

The pending claims cannot be obvious because at the time the invention was made, one of ordinary skill in the art had no reasonable expectation of success in arriving at the claimed invention in view of the cited references. A reasonable expectation of success presupposes that one of ordinary skill in the art is capable of predicting before a research project is initiated – rationally and on the basis of existing knowledge – the successful conclusion of the project within an acceptable time limit. The more unexplored a technical field of research is, the more difficult it is to make predictions about the successful conclusion of the project, and the lower the expectation of success will be. Therefore, in making an assessment of the significance of prior art, one should in an appropriate case take into account the degree to which a reliable prediction

can be made in the field. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). In making this assessment, an examiner also must cast her mind back to the time an invention was made and avoid impermissible hindsight. MPEP § 2141.01 III.

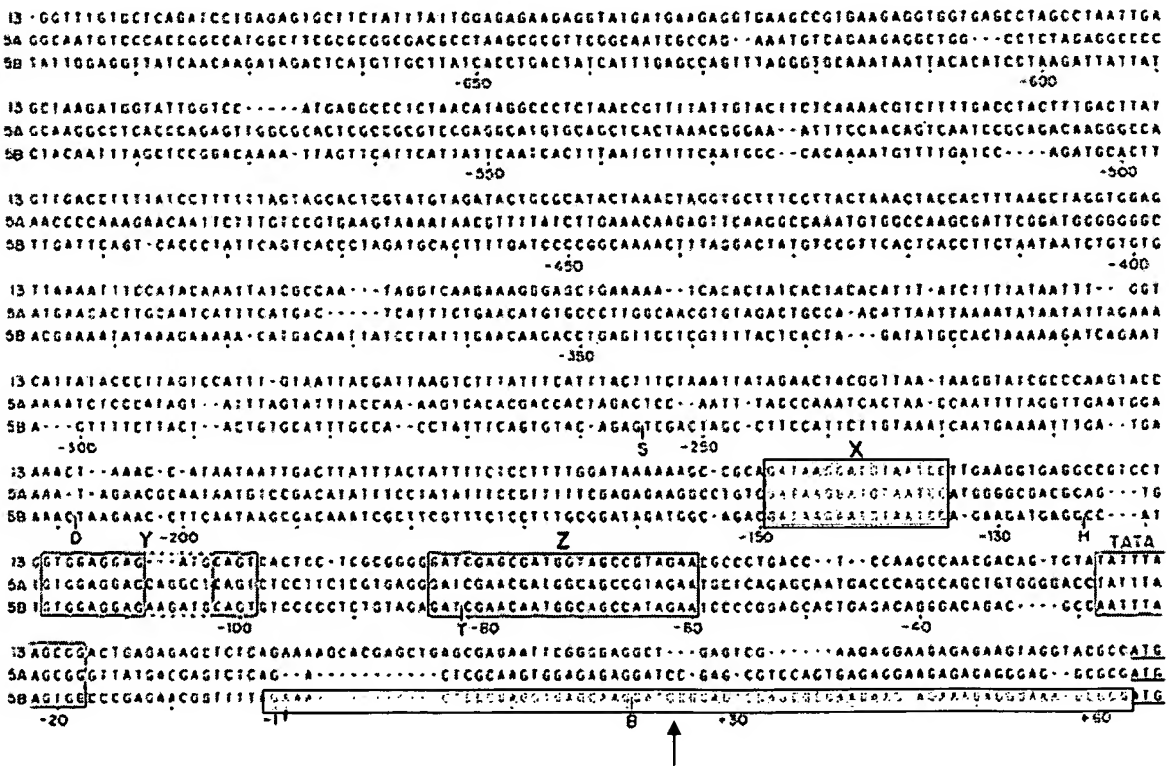
With respect to Stomp *et al.*, Applicants briefly reiterate comments presented in their previous responses. Stomp *et al.* provide general teachings regarding methods of modifying nucleotide sequences to enhance expression in duckweed of encoded, biologically active polypeptides. As the Examiner acknowledges, Stomp *et al.* did not contemplate or disclose using SEQ ID NO:16, as recited in the pending claims, to enhance expression of such encoded polypeptides.

The Examiner cites Buzby *et al.* and Wong *et al.* as bridging the gaps between Stomp *et al.* and the pending claims by guiding one of ordinary skill in the art to any and all ribulose-1,5-bisphosphate carboxylase (rbcS) 5' UTLs, including SEQ ID NO:16. The Examiner alleges that Buzby *et al.* is cited for teaching a 5' UTL comprising SEQ ID NO:16 (Stiekema *et al.* is cited for similar reasons).

While Buzby *et al.* disclose a larger sequence that includes SEQ ID NO:16, Buzby *et al.* teach that a light-regulated nuclear factor (LRF-1) binds to Box X, which is located 150 bp upstream of the transcription start site of rbcS of *Lemna gibba* (Abstract and p. 806 "Footprint Analysis of the Binding Activity" of Buzby *et al.*; supported by Stiekema *et al.*). Buzby *et al.* also teach that the 5' UTLs of three rbcS genes (SSU5A, SSU5B and SSU13) are greater than 60% conserved between nucleotides -300 to +1 and even more conserved in Boxes X, Y and Z (*see*, p. 806 "Identification of a DNA-Binding Activity in Nuclear Extracts" of Buzby *et al.*; *see also*, FIG. 6 and p. 811, second column, second full paragraph, of Buzby *et al.*). However, despite such high sequence homology, Buzby *et al.* observe that LRF-1 does not bind the 5' UTLs equally (*see*, FIG. 6 of Buzby *et al.*). Buzby *et al.* does not contemplate or disclose that SEQ ID NO:16 plays any role in LRF-1 binding. A logical reading of Buzby *et al.* is that the nucleic acid sequences encompassing Box X are required for light-dependent expression in plants from rbcS 5' UTLs (*see*, FIG. 2 of Buzby *et al.*).

The Examiner provides no evidence to support why one of ordinary skill in the art would select SEQ ID NO:16 from Buzby *et al.* Instead, the Examiner provides no more than mere conclusory statements that one of ordinary skill in the art would select SEQ ID NO:16 simply

because it is part of Buzby *et al.*'s entire 5' UTL without explaining how Buzby *et al.*'s teachings of Box X would lead one of ordinary skill in the art to SEQ ID NO:16. Box X does not encompass SEQ ID NO:16, as shown below (FIG. 1 of Buzby *et al.*). Buzby *et al.* only show light-dependent expression from Box X, and does not show any expression from SEQ ID NO:16 alone. Obviousness rejections cannot be sustained by mere conclusory statements, but must be supported by some articulated reasoning with some rational underpinning. MPEP § 2143.01 IV. Instead of focusing on the claimed structure, the Examiner inappropriate relies upon the fact that SEQ ID NO:16 is from a rbcS gene. Because the claimed invention does not require the sequences encompassed in Box X, Applicants amend Claim 82 to recite that the 5' UTL sequence "consists of" SEQ ID NO:16. By this amendment, Box X is necessarily excluded from the claimed 5' UTL sequence.



Moreover, Buzby *et al.* show that one of ordinary skill in the art cannot reliably predict that any sequence from a rbcS 5' UTL enhances polypeptide expression. Box X is nearly 100% identical among the three 5' UTLs, yet light-dependent expression from them was not uniform (*see*, FIG. 6A). Buzby *et al.*, however, made no mention of any region that differed among the three 5' UTLs that may be responsible for the non-uniform expression. Because SEQ ID NO:16 and the related sequences in the other two rbcS 5' UTLs are quite homologous, one of ordinary skill in the art likely would look to other regions of the 5' UTLs or to trans-acting elements to explain the quantitative differences in light-dependent expression. Thus, Buzby *et al.* leave one of ordinary skill in the art to practice undue experimentation as he or she must guess as to which sequences within rbcS 5' UTLs work in connection with Box X, if at all, to drive light-dependent expression.

Wong *et al.* further demonstrate that the art cannot reliably predict that any rbcS 5' UTL, especially SEQ ID NO:16, can be used to enhance polypeptide expression in a plant. Wong *et al.* teach that heterologous polypeptide expression from a rbcS 5' UTL from *Arabidopsis* varies depending upon the promoter, transit peptide coding sequence and heterologous polypeptide coding sequence operably linked thereto. In fact, Wong *et al.* disclose that "the *ats1A* untranslated leader alone yielded slightly higher levels of CryIa(c) protein than the standard polylinker" (*see*, paragraph bridging pp. 90-91 of Wong *et al.*; *see also*, results of vector 10871 v. 10872 in Table 2 of Wong *et al.*). Wong *et al.* also disclose that CryIa(c) increased "when *ats1A* untranslated leader and transit peptide coding sequences are included" (emphasis added; paragraph bridging pp. 85-86 and p. 89, first column, of Wong *et al.*). Wong *et al.* then conclude that "the 5' untranslated leader and the transit peptide together are responsible for the increase in *cryIA(c)* gene expression" (*see*, p. 91 of Wong *et al.*) and that "the ability of 5' untranslated leader sequences and translation fusions to increased gene expression is dependent on the coding sequences to which they are attached" (*see*, *id.*). As such, one of ordinary skill in the art would select not only a rbcS 5' UTL, but also its chloroplast transit peptide coding sequence to enhance polypeptide expression in view of Wong *et al.* The claimed invention, however, does not require chloroplast transit peptide coding sequences. In fact, chloroplast transit peptide sequences would frustrate the purpose of the claimed invention, as no heterologous polypeptide would be secreted into the culture medium (*see*, Claims 93-94).

More importantly, Wong *et al.* did not disclose SEQ ID NO:16. Instead, Wong *et al.* disclose a 5' UTL sequence of TCAGTCACACAAAGAGTAAGAAGAACA. A comparison of the 5' UTL sequence of Wong *et al.* (*see*, FIG. 1 of Wong *et al.*) with SEQ ID NO:16 reveals that the two sequences are structurally distinct (*see*, the alignment below among Wong *et al.*'s 5'UTL and the three 5' UTLs from Buzby *et al.* The sequence denoted "5B" is SEQ ID NO:16). In the alignment, nucleotides in common among the four sequences are highlighted in yellow; whereas additional sequences in common between Wong *et al.*'s 5' UTL and SEQ ID NO:16 are highlighted in green. The 5' UTL of Wong *et al.* has less than 50% homology to SEQ ID NO:16.

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13  GAAAAGCACGAGCTGAGCGAGAATTCGGG-GA-GGCTGAGTCGAAGAGGAAGAGAGAAGTAGGTACGCC 67
5B  GAAACTCCCGAGGTGAGCAAGGATCCGGA-GTCGAGCGCGAAGAAGAGAAAGAGGGAAAGC-------- 60
5A  --GACTCGCAAGTGGAGAGAGGATCCGAGCGTCCAGTGAGAGGAAGAGAGAGGGAGGCGCG-------- 59
Wong----------------------------------TCAGTCACACAAAGAGTAAAGAAGAACA--------- 28
                                         *****  *    *
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In the present case, the structure of the prior art sequences and the claimed sequence are markedly different, so one cannot reasonably predict that their function would be the same. The Examiner provides no more than a mere conclusory statement that one of ordinary skill in the art would select a rbcS 5' UTL without explaining how one could reliably predict increased expression from a sequence have no more than 50% homology to the 5' UTL disclosed in Wong *et al.* Obviousness rejections cannot be sustained by mere conclusory statements, but must be supported by some articulated reasoning with some rational underpinning. MPEP § 2143.01 IV. Instead of focusing on the claimed structure, the Examiner inappropriate relies upon the fact that SEQ ID NO:16 is from a rbcS gene. The Examiner also provides no rationale basis for why one of ordinary skill in the art would select a rbcS 5' UTL when Wong *et al.*'s leader only slightly increased expression (Table 2 of Wong *et al.*). In the absence of sequence similarity between SEQ ID NO:16 and a rationale leading one of ordinary skill in the art from Wong *et al.* to the claimed invention, Applicants submit that one of ordinary skill in the art would not look to Wong *et al.* to enhance protein expression in duckweed as it is not possible to reliably predict the function of SEQ ID NO:16 from Wong *et al.*

The Examiner also errs because a combination ofStomp *et al.*, Buzby *et al.* and Wong *et al.* would not replicate the claimed invention. If indeed one of ordinary skill in the art combined

Stomp *et al.*, Buzby *et al.* and Wong *et al.*, he or she would have a stably transformed duckweed plant culture or duckweed nodule culture transformed with one or more nucleotide sequences encoding a biologically active polypeptide operably linked to Wong *et al.*'s 5' UTL and chloroplast transit peptide coding sequence, as well as Box X. Because of fundamental differences between one of the citations and the claimed invention, one could not recover secreted polypeptides, but instead would have to extract the polypeptide from plant tissue (*i.e.*, chloroplasts).

The Examiner appears to simply pick and choose from the citations only so much of each as will support the given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. This kind of examination is improper, as an obviousness inquiry should look at whether the claimed invention as a whole would have been obvious, not whether the differences themselves would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); and *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). Because none of the cited references contemplate or disclose enhancing polypeptide expression in duckweed with SEQ ID NO:16, in the absence of hindsight reasoning, they cannot render obvious the pending claims.

Because neither Yu *et al.* nor Park *et al.* contemplate or disclose SEQ ID NO:16 to enhance protein expression in duckweed, they cannot render obvious Claim 82 and the claims that depend therefrom. Yu *et al.* disclose a signal peptide for secretion of a protein into medium of plant cell cultures. This cited reference does not contemplate or disclose SEQ ID NO:16. Park *et al.* disclose a signal peptide from rice α-amylase. Likewise, this cited reference does not contemplate or disclose SEQ ID NO:16. Regardless of whether the additional cited references can be combined with Stomp *et al.*, Buzby *et al.* and Wong *et al.*, one of ordinary skill in the art would not arrive at the claimed invention for the reasons noted above. In view of these remarks, Applicants respectfully request withdrawal of the rejections of the claims as obvious over the cited references.

Non-Statutory Obviousness-Type Double Patenting Rejections

The Examiner rejects Claims 82-84 and 87 under the judicially created doctrine of obviousness-type double patenting as patentably indistinct from Claims 16-17 of U.S. Patent No. 6,815,184 to Stomp *et al.* (hereinafter Stomp II) in view of Wong *et al.*, *supra.* This rejection is respectfully traversed

Stomp II provide general teachings regarding methods of modifying nucleotide sequences to increase their expression in duckweed. Stomp II, however, do not contemplate or disclose the use of SEQ ID NO:16, as recited in the pending claims, to enhance expression of a biologically active polypeptide.

Buzby *et al.* does not bridge the gaps between Stomp II and the pending claims by guiding one of ordinary skill in the art to SEQ ID NO:16 to enhance protein expression in duckweed relative to that observed in Stomp II. As noted above, Buzby *et al.* examined DNA binding by LRF-1 in regions of highly related 5' leader sequences of rbcS. Also, Buzby *et al.* is not directed toward protein expression from the highly related 5' leader sequences of rbcS and makes no mention of any importance of the region that includes SEQ ID NO:16 in binding LRF-1. Applicants therefore submit that one of ordinary skill in the art would not look to Buzby *et al.* to enhance protein expression in duckweed in Stomp II when Buzby *et al.* focuses only on the binding activity of LRF-1 to highly related 5' leader sequences of rbcS that do not include SEQ ID NO:16 and when Buzby *et al.* shows that one of ordinary skill in the art could not reliably predict that LRF-1 binds equally. In view of these remarks, Applicants respectfully request that this rejection be withdrawn as applied to Claims 82-84 and 87.

The Examiner then provisionally rejects Claims 82-84 and 97-94 under the judicially created doctrine of obviousness-type double patenting as patentably indistinct from Claims 3, 8-10, 23 and 26-29 of U.S. Patent Application No. 10/794,615. Because this is a provisional rejection, no response is required at this time. However, and as noted in Applicants' previous response, this application and '615 are commonly owned. As such, Applicants will consider the filing of a terminal disclaimer should allowable subject matter be agreed upon in either case and should the Examiner maintain the double-patenting rejection over the '615 patent.

The Examiner then rejects Claims 82-84 and 87 under the judicially created doctrine of obviousness-type double patenting as patentably indistinct from Claims 1-25 of U.S. Patent

Application No. 11/778,480 in view of Wong *et al.*, *supra* and Buzby *et al.*, *supra*. Because Applicants believe this rejection should be a provisional rejection, they submit that no response is required at this time. However, this application and the '480 application are commonly owned. As such, Applicants will consider the filing of a terminal disclaimer should allowable subject matter be agreed upon in either case and should the Examiner maintain the double-patenting rejection over the '480 application.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully submit that the rejections of Claims 82-84 and 97-94 under 35 U.S.C. § 103 should be withdrawn. Accordingly, Applicants submit that this application is in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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